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Acetyl-L-carnitine for the treatment of diabetic peripheral neuropathy (Review)

Rolim LCSP, da Silva EMK, Flumignan RLG, Abreu MM, Dib SA

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[Intervention Review]

Acetyl-L-carnitine for the treatment of diabetic peripheral neuropathy

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ABSTRACT

Background

Diabetic peripheral neuropathy (DPN) is a common and severe complication that affects 50% of people with diabetes. Painful DPN is reported to occur in 16% to 24% of people with diabetes. A complete and comprehensive management strategy for the prevention and treatment of DPN, whether painful or not, has not yet been defined.

Research into treatment for DPN has been characterised by a series of failed clinical trials, with few noteworthy advances. Strategies that support peripheral nerve regeneration and restore neurological function in people with painful or painless DPN are needed. The amino acid acetyl-L-carnitine (ALC) plays a role in the transfer of long-chain fatty acids into mitochondria for β-oxidation. ALC supplementation also induces neuroprotective and neurotrophic effects in the peripheral nervous system. Therefore, ALC supplementation targets several mechanisms relevant to potential nerve repair and regeneration, and could have clinical therapeutic potential. There is a need for a systematic review of the evidence from clinical trials.

Objectives

To assess the effects of ALC for the treatment of DPN.

Search methods

On 2 July 2018, we searched the Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, Embase, LILACS, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform. We checked references, searched citations, and contacted study authors to identify additional studies.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs of ALC compared with placebo, other therapy, or no intervention in the treatment of DPN. Participants could be of any sex and age, and have type 1 or type 2 diabetes mellitus, of any severity, with painful or painless DPN. We accepted any definition of minimum criteria for DPN, in accordance with the Toronto Consensus. We imposed no language restriction.

Pain was the primary outcome, measured as the proportion of participants with at least 30% (moderate) or 50% (substantial) decrease in pain over baseline, or as the score on a visual analogue scale (VAS) or Likert scale for pain.

Data collection and analysis

We followed standard Cochrane methods.

Main results

We included four studies with 907 participants, which were reported in three publications. Three trials studied ALC versus placebo (675 participants); in one trial the dose of ALC was 2000 mg/day, and in the other two trials, it was 1500 mg/day or 3000 mg/day. The fourth trial studied ALC 1500 mg/day versus methylcobalamin 1.5 mg/day (232 participants). The risk of bias was high in both trials of different ALC doses and low in the other two trials.

No included trial measured the proportion of participants with at least moderate (30%) or substantial (50%) pain relief. ALC reduced pain more than placebo, measured on a 0- to 100-mm VAS (MD -9.16, 95% CI -16.76 to -1.57; three studies; 540 participants; P = 0.02; I^2 = 56%; random-effects; very low-certainty evidence; a higher score indicating more pain). At doses of 1500 mg/day or less, the VAS score after ALC treatment was little different from placebo (MD -0.05, 95% CI -10.00 to 9.89; two studies; 159 participants; P = 0.99; I^2 = 0%), but at doses greater than 1500 mg/day, ALC reduced pain more than placebo (MD -14.93, 95% CI -19.16 to -10.70; three studies; 381 participants; P < 0.00001; I^2 = 0%). This subgroup analysis should be viewed with caution as the evidence was even less certain than the overall analysis, which was already of very low certainty.

Two placebo-controlled studies reported that vibration perception improved after 12 months. We graded this evidence as very low certainty, due to inconsistency and a high risk of bias, as the trial authors did not provide any numerical data. The placebo-controlled studies did not measure functional impairment and disability scores. No study used validated symptom scales. One study performed sensory testing, but the evidence was very uncertain.

The fourth included study compared ALC with methylcobalamin, but did not report effects on pain. There was a reduction from baseline to 24 weeks in functional impairment and disability, based on the change in mean Neuropathy Disability Score (NDS; scale from zero to 10), but there was no important difference between the ALC group (mean score 1.66 ± 1.90) and the methylcobalamin group (mean score 1.35 ± 1.65) groups (P = 0.23; low-certainty evidence).

One placebo-controlled study reported that six of 147 participants in the ALC > 1500 mg/day group (4.1%) and two of 147 participants in the placebo group (1.4%) discontinued treatment because of adverse events (headache, facial paraesthesia, and gastrointestinal disorders) (P = 0.17). The other two placebo-controlled studies reported no dropouts due to adverse events, and more pain, paraesthesia, and hyperaesthesias in the placebo group than the 3000 mg/day ALC group, but provided no numerical data. The overall certainty of adverse event evidence for the comparison of ALC versus placebo was low.

The study comparing ALC with methylcobalamin reported that 34/117 participants (29.1%) experienced adverse events in the ALC group versus 33/115 (28.7%) in the methylcobalamin group (P = 0.95). Nine participants discontinued treatment due to adverse events (ALC: 4 participants, methylcobalamin: 5 participants), which were most commonly gastrointestinal symptoms. The certainty of the adverse event evidence for ALC versus methylcobalamin was low.

Two studies were funded by the manufacturer of ALC and the other two studies had at least one co-author who was a consultant for an ALC manufacturer.

Authors' conclusions

We are very uncertain whether ALC causes a reduction in pain after 6 to 12 months' treatment in people with DPN, when compared with placebo, as the evidence is sparse and of low certainty. Data on functional and sensory impairment and symptoms are lacking, or of very low certainty. The evidence on adverse events is too uncertain to make any judgements on safety.

PLAIN LANGUAGE SUMMARY

Acetyl-L-carnitine for the treatment of diabetic neuropathy

The aim of this review

The aim of this review was to assess the effects of acetyl-L-carnitine (ALC) on diabetic peripheral neuropathy (DPN) in people with diabetes. We were particularly interested in whether ALC could relieve pain, and also aimed to identify any harmful effects.

Key messages

We are uncertain whether ALC reduces pain in DPN, as the evidence is sparse and of very low certainty. Adverse events may be no more common than with placebo, but the evidence here is also very uncertain.

What was studied in the review?

Diabetes is a condition where the amount of sugar in the blood is abnormally high. Damage to nerve fibres as a result of diabetes is called DPN. DPN is a frequent and severe complication of diabetes, affecting about 50% of people with long-term diabetes. Overall, 16% to 24% of people with diabetes experience chronic pain due to nerve damage. The feet, legs, and hands are primarily affected by DPN.

There is a need for therapies to restore nerve function and relieve the symptoms of DPN. The Cochrane review authors searched for evidence from randomised trials on the effects of ALC in DPN. Evidence from randomised trials is usually more reliable than other study designs.

The main results of the review

The review authors found four relevant trials, which involved 906 adults with diabetes. Three studies compared ALC with a placebo (an inactive, dummy compound), and one compared ALC with methylcobalamin (a form of vitamin B_{12}).

The certainty of the evidence from the studies ranged from low to very low, which means that we cannot be confident in the findings. The key reasons for this were that results were not always completely or clearly reported, the studies had serious limitations, and the results lacked precision.

In people with nerve damage due to diabetes, it is uncertain whether ALC reduces pain after 12 months of therapy, compared to placebo. The trials provided little or no information on the effects of ALC on functional impairment, sensory testing, and symptoms. Even when trials provided data, the quality of evidence was too low to draw reliable conclusions. The study that compared ALC with methylcobalamin did not assess pain. Functional impairment and symptoms may improve to a similar extent with ALC and methylcobalamin.

Harmful side effects may be no more frequent with ALC than with placebo. The evidence on adverse events from the trial comparing ALC with methylcobalamin was very uncertain.

Two of the four studies were funded by a manufacturer of ALC and the other two studies had at least one co-author who was a consultant for an ALC manufacturer.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Acetyl-L-carnitine compared to placebo for the treatment of diabetic polyneuropathy

Acetyl-L-carnitine compared to placebo for the treatment of diabetic peripheral neuropathy (DPN)

Patient or population: people with diabetic peripheral neuropathy
Settings: outpatient
Intervention: acetyl-L-carnitine (ALC; 1500 mg/day to 3000 mg/day)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Placebo	Acetyl-L-carnitine			
Pain at 6 months or more; all doses Assessed by change from baseline, using a 0- to 100-mm VAS, where higher scores indicate more pain) Follow-up: 12 months	The control group baseline average VAS score was 49.2[a] The average improvement in the control groups was 10.4 points	The mean VAS pain score improved on average 9.16 points more (1.57 to 16.76 points more) than in the placebo group	540 (3 RCTs)	⊕⊝⊝⊝ **Very low** [b,c,d,e]	
Functional impairment and disability Assessed by NIS or NDS at 6 months or more	Included studies did not measure this outcome.				
Impairment of sensation Assessed by quantitative sensory testing - vibration perception threshold - at 6 months or more Follow-up: 12 months	The group that received ALC 3000 mg/day had better vibration perception than the placebo group.		341 2 RCTs	⊕⊝⊝⊝ **Very low**[d,f]	The 2 RCTs that measured this outcome did not provide complete data. Not measured in a 3rd trial
Impairment of sensation Assessed by quantitative sensory testing - thermal threshold - at 6 months or more	Included studies did not measure this outcome.				
Symptom quality and severity	Although 2 other studies assessed symptoms, the scale used was not validated. A 3rd study did not assess symptom quality and severity.				

Assessed by change in symptom score on a validated screening questionnaire (NSS or MNSI) at 6 months or more Follow-up: 12 months			
Adverse events: any adverse event, adverse events requiring withdrawal, and serious adverse events Follow-up: 12 months	1 study found no clear difference in withdrawals in the intervention group (4.1%) compared with the placebo group (1.4%, P = 0.17). 1 study reported no dropouts due to adverse events, and less pain (P = 0.026), paraesthesia (P = 0.023), and hyperaesthesias (P = 0.025) in the 3000 mg/day ALC group than the placebo group. 1 study provided no numerical data.	540 (3 RCTs)	⊕⊕⊝⊝ **Low**[c,g]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ALC: acetyl-L-carnitine; **CI**: confidence interval; **MNSI**: Michigan Neuropathy Screening Instrument; **NDS**: Neuropathy Disability Score; **NIS**: Neuropathy Impairment Score; **NSS**: Neuropathy Symptom Score; **RCT**: randomised controlled trial; **VAS**: visual analogue scale

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[a]Mean baseline scores from included studies (score estimated from a graph in De Grandis 2002).

[b]Downgraded one level for indirectness: the outcome is indirectly related to the function of the intervention (ALC does not have a direct effect on pain relief), and we were unable to report the outcome as specified (i.e. the number with 30% pain relief).

[c]Downgraded one level due to imprecision: the CI included the possibility of both a clinically important effect and little or no effect.

[d]Downgraded one level for study limitations, due to an unclear risk of bias in three included studies in several domains. Sima 2005a, and Sima 2005b did not fully describe methods of randomisation, allocation concealment, or blinding. De Grandis 2002 was at an unclear risk of bias from attrition and blinding of outcome assessors. We also assessed the selection of participants for measurement of pain at unclear risk of bias.

[e]Heterogeneity in the pain analysis was substantial (I^2 = 56% and differences between participants). This might be explained by differences in effect between ALC ≤ 1500 mg/day and > 1500 mg/day subgroups.

[f]Downgraded two levels: in the absence of numerical data, the outcome was at high risk of reporting bias, and precision could not be assessed. The two trials were not reported separately and we do not know if the results were consistent. We must therefore be very uncertain about the estimate.

[g]Downgraded one level for reporting bias, as one trial did not provide data.

Summary of findings 2. Acetyl-L-carnitine compared to methylcobalamin for the treatment of diabetic polyneuropathy

Acetyl-L-carnitine compared to methylcobalamin for the treatment of diabetic peripheral neuropathy

Patient or population: the treatment of diabetic peripheral neuropathy
Setting: outpatients, China
Intervention: acetyl-L-carnitine (ALC, ≤ 1500 mg/day)
Comparison: methylcobalamin (0.5 mg three times per day)

Outcomes	**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with methylcobalamin	**Risk with acetyl-L-carnitine**				
Pain at 6 months or more	Included study did not measure this outcome.					
Functional impairment and disability Assessed by change in NDS score (range of possible scores from 0 (normal function) to 10 (maximal disability) Follow-up: 24 weeks	The methylcobalamin group baseline average NDS score was 6.43. The average improvement in the methylcobalamin group was 1.35 points.	The average NDS score improved 0.31 more in the ALC group than in the methylcobalamin group (0.15 less to 0.77 more).	-	232 (1 study)	⊕⊕⊝⊝ **Low**[a,b]	
Impairment of sensation: quantitative sensory testing - vibration perception threshold - at 6 months or more	Included study did not measure this outcome.					
Impairment of sensation: quantitative sensory testing - thermal threshold - at 6 months or more	Included study did not measure this outcome.					
Symptom quality and severity Assessed by NSS score (range of possible scores 0 to 9; higher scores indicate more symptoms) Follow-up: 24 weeks	The methylcobalamin group baseline average NSS score was 6.37 The average change (decrease) in the methylcobalamin group was 2.11 points.	The average NSS score improved 0.24 more in the ALC group than in the methylcobalamin group (0.37 less to 0.85 more).	-	232 (1 study)	⊕⊕⊝⊝ **Low**[a,b]	
Adverse events	287 per 1000	290 per 1000 (195 to 436)	RR 1.01 (0.68 to 1.52)	232 (1 study)	⊕⊕⊝⊝ **Low**[a,c]	

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ALC: Acetyl-L-carnitine; **CI**: confidence interval; **NDS**: Neuropathy Disability Score; **NIS**: Neuropathy Impairment Score; **NSS**: Neuropathy Symptom Score; **RCT**: randomised controlled trial; **VAS**: visual analogue scale

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded once for indirectness, as the control intervention methylcobalamin is not an established treatment for DPN and its effects are uncertain.
[b]Downgraded once for imprecision: the CI included the possibility of both a clinically important effect and little or no effect; small sample (232 participants).
[c]Downgraded once for indirectness, as the comparator made it difficult to distinguish the adverse effects of ALC.

BACKGROUND

Description of the condition

Diabetic peripheral neuropathy (DPN) is the most common chronic complication of diabetes mellitus, affecting approximately 50% of people with diabetes (Tesfaye 2010). The internationally accepted definition of DPN used in clinical practice is "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes, after the exclusion of other causes" (Boulton 2005a).

DPN is frequently asymptomatic but it may be clinically evident through a set of positive and negative symptoms. The positive symptoms are often painful and the negative are abnormalities associated with lack of sensation or, less commonly, with weakness. Chronic neuropathic pain, depression, balance disorders, foot ulceration, Charcot's arthropathy, osteomyelitis, and amputations are some examples of complications associated with progressively advanced stages of DPN (Callaghan 2012).

A combination of neuropathic symptoms, signs, and abnormal electrical diagnostic studies provides researchers with the most accurate diagnosis of peripheral neuropathy (England 2005; Tesfaye 2010). However, in clinical practice, the diagnosis of DPN is made after a careful clinical examination, with at least two neurological tests. For example, the combination of abnormal temperature and vibration tests on neurological examination of a person with diabetes has 87% sensitivity in detecting DPN (Boulton 2005a).

In painful DPN, the pain is typically distal, symmetrical, and worsens at night. There are five different phenotypes of pain in DPN: (1) evoked pain (allodynia or hyperalgesia); (2) paroxysmal pain (electric shock, sharp); (3) deep pain (compression, tightness); (4) superficial pain (burning); and (5) paraesthesia and dysaesthesia (tingling, brushing) (Rolim 2017). On examination, it is possible to observe hyperalgesia (abnormal sensitivity to painful stimuli) and allodynia (heightened sensitivity to non-noxious stimuli), as well as hypoalgesia. The prevalence of neuropathic pain is difficult to ascertain, as definitions vary enormously among studies. It is thought that between 16% and 24% of people with DPN may experience chronic neuropathic pain (Boulton 2010). In clinical trials, the severity of pain is evaluated through pain scales (visual analogue scale (VAS) and 11-point Likert scale), and outcomes must be evaluated through validated instruments (for example, the Brief Pain Inventory, McGill Pain Questionnaire, or the Quality of Life in Neurological Disorders assessment tool) (Cruccu 2004). The usual criteria for including a person with DPN in a trial of painful diabetic neuropathy are the presence of DPN associated with neuropathic pain lasting for three months or longer, and a mean weekly pain level between 40 and 100, measured on a 0- to 100-mm VAS.

A long period of hyperglycaemia, metabolic imbalances such as oxidative stress, mitochondrial dysfunction, neuroinflammation, accumulation of advanced glycation end-products, and dyslipidaemia (an increase in low density lipoprotein (LDL) and triglycerides, and a decrease in high density lipoprotein (HDL)) are the main factors associated with the development of DPN. However, overall hyperglycaemic exposure seems to be the most important factor associated with DPN (Tesfaye 2010). The elucidation of metabolic disruptions related to hyperglycaemia remains the foremost target for research, with the aim of reversing or minimising these homeostatic imbalances, and eventually reducing complications and negative impacts on quality of life in persons with DPN.

Apart from tight blood glucose control in type 1 diabetes mellitus, no treatments have shown any capacity to arrest DPN progression. In addition, the pharmacological treatment of painful DPN remains a challenge for physicians, and the ability of the individual to tolerate treatment remains a major consideration in any treatment decision (Ziegler 2009). A multifaceted treatment approach to chronic neuropathic pain in DPN is reasonable but results, even in the best RCTs, have been modest so far (Rolim 2017). Currently, there are many treatments for painful DPN, but adverse effects can limit their utility (Bril 2011), and very few papers have studied the effects of treatment on function and quality of life.

Description of the intervention

Acetyl-L-carnitine is a naturally occurring amino acid that is sometimes used as a dietary supplement. In humans, the metabolic pool of carnitine comprises nonesterified levo-carnitine (L-carnitine) and acyl carnitine esters. Of these, acetyl-L-carnitine (ALC) forms the greatest component. Three mechanisms control carnitine homeostasis: absorption from diet, a limited rate of synthesis, and effective renal reabsorption (Rebouche 2004). ALC is produced in the kidneys, central nervous system and liver, via the action of ALC-transferase, and is stored in skeletal muscle. ALC plays an essential role in the transfer of long-chain fatty acids into the mitochondria for β-oxidation (Sima 2007). ALC supports cell metabolism during hypoxia from, for example, reduced circulation, or due to genetic metabolic defects. Binding of organic acids and fragmented free fatty acids by ALC enables their expulsion from the cell and prevents them from harming cell and tissue structures.

In addition, ALC is able to reduce the concentration of tumour necrosis factor alpha, and has an antioxidant effect on mitochondrial DNA, whilst stimulating mitochondrial DNA synthesis. Therefore, ALC not only assists in the transportation of long-chain fatty acids through the inner mitochondrial membrane for β-oxidation, but also has a role in energy availability and prevents toxic accumulation of long-chain fatty acids (Williamson 1992).

ALC can be administered orally, intravenously, or intramuscularly. Oral doses range from 1500 mg to 3000 mg per day, in divided doses. Intravenous and intramuscular doses range from 1000 mg to 2000 mg daily. These doses result in physiologically meaningful blood levels (Anon 2010).

How the intervention might work

Clinical trials, usually in people with an advanced stage of DPN, have shown disappointing outcomes from experimental treatments based on vitamin supplementation, aldose reductase inhibitors, and protein kinase C inhibitors (Boulton 2010; Wong 2007). In these studies, each drug has targeted a single underlying pathogenic factor. By contrast, ALC potentially targets several mechanisms to reduce disease progression (Sima 2007).

In experimental diabetic neuropathy, as well as in human diabetic neuropathy, ALC is depleted in peripheral nerves (Scarpini 1996). Replenishment of ALC enhances regional blood flow, increases myo-inositol and free carnitine levels, and reduces malonyl dialdehyde (that is, reduces lipid peroxidation).

Why it is important to do this review

Peripheral neuropathy is a frequent, polymorphic, and devastating complication associated with diabetes mellitus, characterised by debilitating symptoms. In addition, it is associated with an increased risk of other complications, in particular, those involving the cardiovascular system and the foot (Rolim 2009). The World Health Organization (WHO) estimates that "every 30 seconds a lower limb is lost somewhere in the world as a consequence of diabetes" (Boulton 2005b).

There are over 415 million adults with diabetes in the world. Of these, approximately half have DPN, and 16% to 24% have chronic painful DPN (Boulton 2010). Of those with chronic painful DPN, up to 39% have never received any kind of treatment for their pain (Daousi 2004). Other than excellent diabetic control, there are no known modulators of neuropathy occurrence or progression. Therefore, there is a substantial worldwide burden of disease, and an unmet need for prevention and treatment of DPN and its complications, including chronic neuropathic pain, the diabetic foot, and amputation.

At least four systematic reviews and meta-analyses have been published about ALC or L-carnitine and their effects on different conditions: type 2 diabetes mellitus (Vidal-Casariego 2013), secondary prevention of cardiovascular disease (DiNicolantonio 2013), hepatic encephalopathy (Jiang 2013), end-stage renal failure under haemodialysis (Chen 2014), with positive results in all except renal failure. ALC has been reported to show promise as a therapeutic agent for DPN in a small number of studies and reviews (Li 2015; Veronese 2017), but this is the first Cochrane Systematic Review of ALC for DPN.

OBJECTIVES

To assess the effects of acetyl-L-carnitine (ALC) for the treatment of diabetic peripheral neuropathy (DPN).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs with parallel or cross-over designs.

Quasi-RCTs are studies in which participants are allocated to intervention groups using methods that aim to be random, but which are potentially predictable, such as assignment based on hospital number or date of birth.

Types of participants

People of any sex and age (adults, including those over 60 years, and children), with either form of diabetes (type 1 or type 2). Diabetic participants could have any severity of DPN (for example, stages from Grade 0 to Grade 5 described by Dyck 1988) and any of the three definitions of minimal criteria for typical DPN, as recommended by the Toronto Consensus (Tesfaye 2010), that is, probable, confirmed, or subclinical DPN.

We considered that trials in participants with only symptoms or signs of DPN (i.e. with 'probable DPN') provided a lower certainty of evidence.

Types of interventions

ALC compared with placebo, other treatment, or no intervention. Where additional treatments were given, these must have been matched equally in the intervention and control groups.

Types of outcome measures

The outcomes listed were not eligibility criteria for the review, but were the outcomes of interest in whichever studies were included.

Primary outcomes

Pain: measured using a validated scoring system such as a visual analogue scale (VAS) or numerical rating scale reported as the proportion of participants with at least 30% (moderate) pain relief over baseline or 50% (substantial) pain relief over baseline or as a continuous outcome on a VAS or Likert scale (Cruccu 2004). The time scale was six months (at minimum) after treatment, and, when possible, at a year or even two or more years after treatment.

We used pain as the primary outcome measure because a significant proportion of people with diabetes have painful DPN, it causes significant ill health and disability, and many trials use pain as a surrogate measure of disease severity.

Secondary outcomes

- **Functional impairment and disability**: assessed by change in the Neuropathy Impairment Score (NIS) (Dyck 1988) or the Neuropathy Disability Score (NDS) (or one of the modified NDS scores) in the lower extremities (Young 1993), at a minimum of six months after treatment. We considered these outcomes as continuous variables (for example, score on a scale of zero to 10 for the modified NDS).
- **Impairment of sensation**: assessed by changes in quantitative sensory testing (vibration perception threshold and thermal threshold), at a minimum of six months after treatment.
- **Quality of life**: assessed by changes in scores on a validated questionnaire, such as the 36-item Short Form Health Survey (SF-36) or the Quality of Life in Neurological Disorders (NeuroQol) assessment tool (Vileikyte 2003), at a minimum of six months after treatment.
- **Neurophysiological measures**: assessed by changes in sural and peroneal nerve conduction velocities (NCVs) and changes in amplitude of either the sensory nerve action potential (SNAP) or the compound muscle action potential (CMAP) of the ulnar, peroneal, and tibial nerves after an appropriate duration of therapy (one year or more).
- **Adverse events**: any adverse event, adverse events requiring withdrawal, and serious adverse events (those that are fatal, life-threatening, or require prolonged hospitalisation).
- **Symptom quality and severity**: assessed by changes in scores on validated screening questionnaires, such as the Neuropathy Symptom Score (NSS) or Michigan Neuropathy Screening Instrument (MNSI), at a minimum of six months after treatment. These instruments were continuous variables (e.g. from zero to 9 for NSS) (Young 1993).
- **Sural nerve biopsy parameters**: including quantification of axon numbers and density and of regeneration clusters.

The secondary outcomes were assessed six months (at minimum) after treatment, and, when possible, at a year or even two or more years after treatment.

Search methods for identification of studies

Electronic searches

We searched the following databases:

- the Cochrane Neuromuscular Specialised Register via Cochrane Register of Studies (CRS-Web; searched 2 July 2018; Appendix 1);
- the Cochrane Central Register of Controlled Trials (CENTRAL) via CRS-Web (searched 2 July 2018; Appendix 2);
- MEDLINE Ovid (1946 to 2 July 2018; Appendix 3);
- Embase Ovid (1974 to 2 July 2018; Appendix 4);
- LILACS iAHx (Latin American and Caribbean Health Science Information database; 1982 to 2 July 2018; Appendix 5);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/; 2 July 2018; Appendix 6);
- World Health Organization International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/en/; 2 July 2018; Appendix 7).

We imposed no restriction on language of publication.

Searching other resources

We checked all references in the identified trials and contacted trial authors to identify any additional published or unpublished data. We checked all references in any identified review articles.

We searched the websites of relevant manufacturers for trial information.

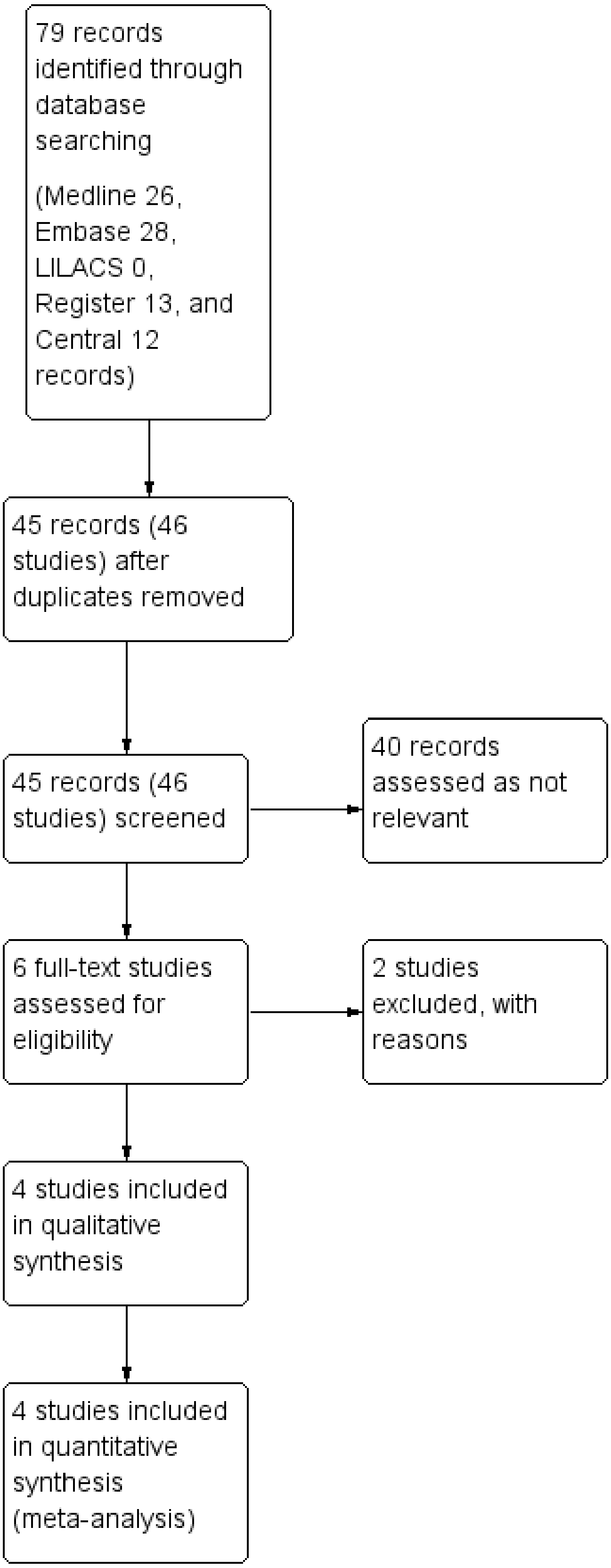
We also searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed), and reported the date in such cases.

Data collection and analysis

Selection of studies

Two review authors (LCSPR and EMKS) independently screened the trials identified by the literature search for inclusion in this review. They then retrieved the full-text reports or publications of potentially eligible studies. They identified and excluded duplicates, and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review. The same two review authors independently screened the full text, identified whether studies met the inclusion criteria, and identified and recorded the reasons for exclusion of ineligible studies. They consulted the other review authors (RLGF, MMA, and SAD) if there was any disagreement (at this or at any other stage listed below). In the event of disagreement, the review authors included trials only when we reached a consensus. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1) and the 'Characteristics of excluded studies' table.

Figure 1. PRISMA flow chart illustrating the study selection process for the review.



Data extraction and management

Two review authors (LCSPR and EMKS) independently extracted data. They resolved discrepancies in the results by discussion with the review team (RLGF, MMA, and SAD). They used a standard form to extract the following information:

- Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
- Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline characteristics, inclusion criteria, and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications, and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported, as described above.
- Notes: funding for trial, and notable conflicts of interest of trial authors.
- Outcome data.

We collected both continuous and dichotomous data as recorded by the primary investigators. If the paper did not report outcome data in a usable way, we noted this in the 'Characteristics of included studies' table. One review author (EMKS) transferred data into Review Manager 5 (RevMan 2014). Two other review authors (LCSPR and RLGF) checked the outcome data entry. The review team (LCSPR, MMA, and SAD) spot-checked study characteristics against the trial report for accuracy.

If in future versions of this review reports require translation, either the translator will extract data directly using a data extraction form, or the review authors will extract data from the translation provided. After data entry, where possible, a review author will check numerical data from translated trials against the study report.

Assessment of risk of bias in included studies

Two review authors (LCSPR and EMKS) independently assessed the risk of bias in the studies that were included in this review according to the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). They resolved any conflicts by discussion with the rest of the review team (RLGF, MMA, SAD).

Where information on risk of bias related to unpublished data or correspondence with a trial author, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that specific outcome. We followed the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* on summary 'Risk of bias' assessments (Higgins 2017).

- Low risk of bias: low risk of bias for all key domains.
- Unclear risk of bias: unclear risk of bias for one or more key domains.
- High risk of bias: high risk of bias for one or more key domains.

Assesment of bias in conducting the systematic review

We conducted the review according to the published protocol (Rolim 2014), and reported any deviations from it in the Differences between protocol and review section.

Measures of treatment effect

For dichotomous variables, we calculated the risk ratio (RR) and 95% confidence interval (CI). For continuous outcomes, we calculated the mean difference (MD) and 95% CI when studies used the same unit of measurement for a variable. If studies measured continuous data for a variable using different instruments (different units of measurement that were not interchangeable), we would have pooled these data using the standardised mean difference (SMD). Where possible, we analysed continuous scales together. When it was not possible to combine data in this way, we dichotomised results to improvement versus no improvement or worsening, and calculated risk ratios (RRs). If the authors of the primary studies did not make the necessary information available, we planned to display any non-parametric data (for example, effects reported with medians and quartiles) or data without sufficient statistical information (for example, missing standard deviations or numbers of participants) in an 'Additional table'.

Unit of analysis issues

The unit of analysis was based on the individual participant, that is, the number of observations in the analysis matched the number of individuals randomised. In future versions of this review, if we identify trials with a cross-over design, we will use only first period data (the period before participants cross over to the alternative treatment) (Elbourne 2002).

When multiple trial arms were reported in a single trial, we included only the arms or participants relevant to the review question. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) were combined in the same meta-analysis, we halved the control group to avoid double-counting.

Dealing with missing data

Regardless of the type of data, we reported dropout rates in the `Characteristics of included studies' table, used intention-to-treat (ITT) analysis when possible, and specified any different analyses (Higgins 2011).

We tried to contact all trial authors for clarification of missing data. However, we did not receive any responses.

Assessment of heterogeneity

We measured inconsistency among the pooled estimates using the I^2 test ($I^2 = [(Q - df)/Q] \times 100\%$), where Q is the Chi^2 statistic and df is degrees of freedom. The I^2 statistic is a measure of the percentage of variability in effect estimates resulting from heterogeneity rather than sampling error (Deeks 2017; Higgins 2003).

As strict thresholds for interpretation of I^2 are not recommended, we followed the rough guide to interpretation in the*Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity

- 75% to 100%: considerable heterogeneity

When I^2 lay in an area of overlap between two categories (e.g. between 50% and 60%), we considered differences in participants and interventions among the trials contributing data to the analysis (Deeks 2017).

Assessment of reporting biases

If future versions of the review include a sufficient number of studies (more than 10), we will assess publication bias by drawing a funnel plot (trial effect versus trial size) (Higgins 2011). We could not draw a funnel plot because the number of included studies was insufficient.

Data synthesis

Qualitative information

We reported qualitative information relative to methods, risk of bias, description of participants, and outcome measures in the 'Characteristics of included studies' tables. We did not include qualitative (non-randomised) studies in the review.

Quantitative information

We would have used a fixed-effect model in the meta-analysis of studies that were very homogeneous, that is, in which the characteristics of the design, population, interventions, comparators, and outcomes were similar. However, we used a random-effects model, as the included trials were heterogeneous (Deeks 2017).

The two comparisons were not suitable for combination and we reported their results separately.

'Summary of findings' table

We created `Summary of findings tables' for all comparisons and included the following prespecified outcomes (reported at a minimum of six months after treatment).

- **Pain**: measured using a validated scoring system such as a VAS or numerical rating scale, reported preferably as the proportion of participants with at least 30% (moderate) pain relief over baseline.
- **Functional impairment and disability**: assessed by change in the NIS or NDS in the lower extremities.
- **Impairment of sensation**: assessed by the change in a quantitative sensory test - vibration perception threshold.
- **Impairment of sensation**: assessed by the change in a quantitative sensory test - thermal threshold.
- A**dverse events**: any adverse event, adverse events requiring withdrawal, and serious adverse events.
- **Symptom quality and severity**: assessed by the change in score on a validated screening questionnaire (NSS or MNSI).

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence (studies that contributed data to the prespecified outcomes). We used the methods and recommendations described in Chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* using GRADEpro software (GRADEpro GDT; Schünemann 2011a; Schünemann 2011b). We downgraded our certainty in the evidence once if any single GRADE consideration applied to a serious degree and twice if very serious. We justified all decisions to downgrade or upgrade the certainty of the evidence in footnotes, and we made comments to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

If we found substantial heterogeneity, we investigated the possible causes by exploring the impact of risk of bias and participant characteristics. If we found sources of heterogeneity, and if there were sufficient data, we conducted meta-analysis by subgroups (for example, by dosage, participant age, and type of diabetes):

- dosage: ≤ 1500 mg ALC daily for oral doses and ≤ 1000 mg daily for intravenous or intramuscular doses versus > 1500 mg oral ALC daily or > 1000 mg for intravenous or intramuscular doses (cut-off based on half of the maximum dosage of ALC (3000 mg/day orally and 2000 mg/day intravenously) (Anon 2010);
- age: since the presence of DPN depends directly on elevated glycaemic levels (Tesfaye 2010), there may be a stronger relationship between the prevalence of DPN and older age;
- type of diabetes: type 1 or type 2.

According to sections 9.6.6 and 9.6.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions*, and because only two subgroups were available, we considered the results of subgroups by interpreting the tests for subgroup differences (Deeks 2017).

Sensitivity analysis

In future versions of this review, if there are an adequate number of studies, we will perform sensitivity analyses to explore the robustness of the results. We will repeat the analysis excluding studies:

- that are unpublished;
- at high risk of bias;
- that assess outcomes after less than six months' treatment;
- that include participants with 'probable' DPN according to the Toronto Consensus (Tesfaye 2010)).

Economics issues

We did not find sufficient economic data in the included studies, but in future versions of this review, if cost data are available, we will report them.

RESULTS

Description of studies

Results of the search

Our searches identified 79 records from the following databases: Cochrane Neuromuscular Specialised Register 13, Cochrane Central Register of Controlled Trials (CENTRAL) 12, MEDLINE 26, Embase 28, and Latin American and Caribbean Health Science Information database (LILACS) 0. From the 79 initial references, removal of duplicates resulted in 45 records. We assessed 40 records as not relevant for this review. We assessed the full text of the six other studies for eligibility. We excluded two studies for defined reasons (see Characteristics of excluded studies), and included four studies for analysis. See Figure 1 for a PRISMA chart illustrating the study selection process.

Included studies

See the Characteristics of included studies section.

Study characteristics

We included four studies, with a total of 907 participants (De Grandis 2002; Li 2016; Sima 2005a; Sima 2005b). These studies provided data for two different comparisons:

- acetyl-L-carnitine (ALC) versus placebo (675 participants; De Grandis 2002, Sima 2005a; Sima 2005b)
- ALC versus methylcobalamin (232 participants; Li 2016)

Only one study provided information about the period over which it was conducted (between August 2008 and March 2011) (Li 2016).

Three studies were multicenter RCTs (De Grandis 2002; Sima 2005a; Sima 2005b). Sima 2005a and Sima 2005b reported data from two different clinical trials in the same paper. Li 2016 was a multicenter non-inferiority randomised trial that compared ALC with methylcobalamin without a placebo comparison.

Setting

A single paper reported the results from two multicentre studies with identical methods: one performed in the USA and Canada (Sima 2005a), and the other in the USA, Canada, and Europe (Sima 2005b). The two other trials were each performed in a single country: De Grandis 2002 enrolled participants from 20 centres in Italy, Li 2016 enrolled participants from eight centres in China.

Participants

Participants included men and women, with an age range from 18 to 70 years old or more. Two studies included a preponderance of older adults (De Grandis 2002; Li 2016). In De Grandis 2002, 50.2% were women, whereas Li 2016 had a slight preponderance of men (52.5%). Sima 2005a and Sima 2005b did not provided detailed information about age and gender. Participants with either type 1 or type 2 diabetes who met clinical and/or neurophysiological criteria for DPN were eligible for all studies.

Since Sima 2005a presented incomplete data regarding the number of participants; we could not determine the number of participants analysed in each group for the majority of outcomes. We contacted the trial authors for clarification, but did not receive an answer.

Sample size

De Grandis 2002 included 333 participants, Li 2016 included 232 participants, and Sima 2005a and Sima 2005b together included 342 participants, but the paper did not specify the numbers in each study. Sima 2005a and Sima 2005b did not evaluate all outcomes in all 1335 participants who were randomised. The numbers of participants from Sima 2005a and Sima 2005b included in Analysis 1.1 were considerably smaller than the numbers of participants randomised. Pain was measured only in participants who reported pain as their most bothersome symptom at baseline (342/1335; 25.6%). The study reported sural nerve biopsy findings in 87% of the participants who underwent a baseline biopsy (245 evaluable pairs of biopsies) and limited the analysis to participants from US and Canadian centres, excluding European centres. Only Li 2016 provided information about power and sample size calculation.

Interventions

The four included studies administered ALC orally at different dosages and for different periods:

- 1500 mg/day (for 24 weeks in Li 2016 and for one year in Sima 2005a and Sima 2005b);
- 2000 mg/day (for 355 days in De Grandis 2002);
- 3000 mg/day (for one year in Sima 2005a).

De Grandis 2002 started the intervention with intramuscular ALC at a dosage of 1000 mg/day for 10 days, and continued ALC orally as described above.

Outcomes

Three of four included studies reported the review primary outcome (pain) as an end point (De Grandis 2002; Sima 2005a; Sima 2005b). Only Li 2016 used a validated neuropathy functional impairment or disability scale (the Neuropathy Disability Score) or a validated symptom quality and severity scale (the Neuropathy Symptom Score). Only Sima 2005a and Sima 2005b reported quantitative sensory testing and sural nerve biopsy parameters. None of the included studies reported quality of life. All trials evaluated neurophysiological measures (nerve conduction velocities (NCVs) and sensory and motor nerve amplitudes), and adverse events.

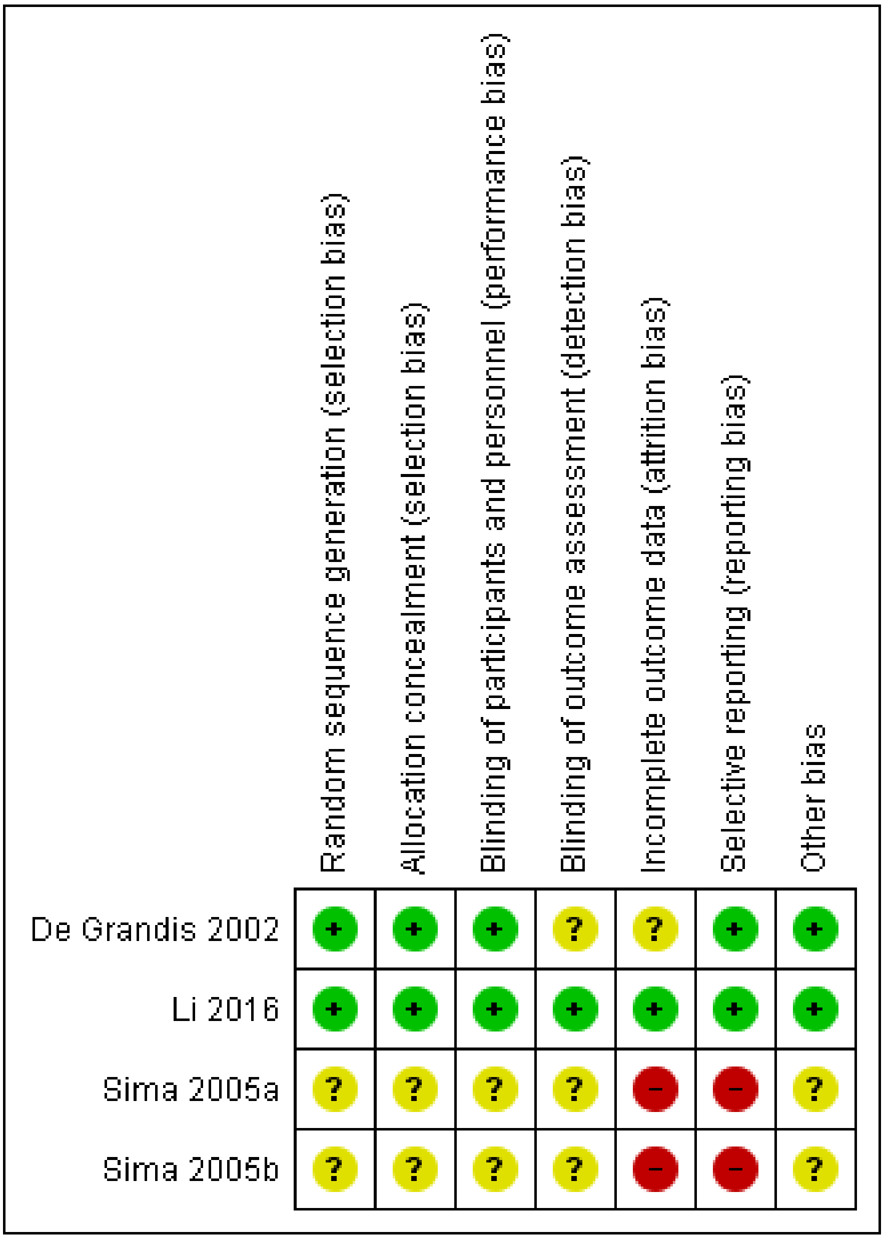
Excluded studies

We excluded two studies. In the first study, the purpose of the intervention was to prevent foot ulceration (Abbott 1997). The second was a pilot study with a very small number of participants (20) and a duration of only 15 days (Quatraro 1995). See Characteristics of excluded studies.

Risk of bias in included studies

We presented the risk of bias of each included study in the 'Characteristics of included studies' tables. Figure 2 summarises the review authors' 'Risk of bias' judgments for all included studies. We judged two studies at low risk of bias (De Grandis 2002; Li 2016) and the other two studies at high risk of bias (Sima 2005a; Sima 2005b).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Green (+) = low risk of bias; yellow (?) = unclear risk of bias; red (-) = high risk of bias.



Allocation

Two studies reported methods of randomisation and allocation concealment and we rated them at low risk of bias (De Grandis 2002; Li 2016). The other two studies did not report these procedures and we rated them at unclear risk of bias (Sima 2005a; Sima 2005b).

Blinding

Participants and investigators were blinded to the interventions in Li 2016, which we rated at low risk of bias. We rated Sima 2005a and Sima 2005b at unclear risk of performance and detection bias, as there was insufficient information about blinding. De Grandis 2002 did not provide information on assessor blinding, for which we judged it at unclear risk of detection bias.

Incomplete outcome data

De Grandis 2002 reported a loss to follow-up of 11.7% (39/333), with no clear mention of ITT analysis. Although it is probable that De Grandis 2002 performed an ITT analysis, because they reported something as 'overall clinical evaluation, which included all patients randomised', we rated this study as unclear risk of bias. In Li 2016, there was a 12% loss to follow-up (28/232), with an ITT analysis; thus, we rated this study at low risk of bias. In Sima 2005a and Sima 2005b, of 1335 randomised participants, only those who received at least one dose of study medication and had one valid post-randomisation electromyographic assessment were included in the analysis. Sural nerve biopsies were performed only in participants from North American Centres. Of these participants, 87% (245/282) provided an evaluable pair of biopsies. Since these participants differed from the European participants in important ways (e.g. they had a shorter duration of diabetes, were heavier, a smaller proportion had type I diabetes, and a greater proportion were people of colour), this represented a high risk of bias.

Selective reporting

Two studies reported all prespecified outcomes and we rated them at low risk of bias (De Grandis 2002; Li 2016). Most outcomes from the two trials reported in the single paper were not reported separately. Reporting was incomplete, for example, because in the analyses of outcomes other than pain and adverse events, the trial authors presented incomplete data. Therefore, we rated these studies at high risk of bias (Sima 2005a and Sima 2005b).

Other potential sources of bias

De Grandis 2002 and Li 2016 appeared to be free from other sources of bias. Pain was investigated in only a proportion of the participants in Sima 2005a and Sima 2005b (those who reported pain as their most bothersome symptom). As it is unclear whether blinding and allocation concealment were adequate, knowledge of intervention groups could, in principle, have influenced inclusion of participants in the pain analysis. We rated these studies at unclear risk of bias in relation to the effects of ALC on pain.

Effects of interventions

See: **Summary of findings for the main comparison** Acetyl-L-carnitine compared to placebo for the treatment of diabetic polyneuropathy; **Summary of findings 2** Acetyl-L-carnitine compared to methylcobalamin for the treatment of diabetic polyneuropathy

Acetyl-L-carnitine versus placebo

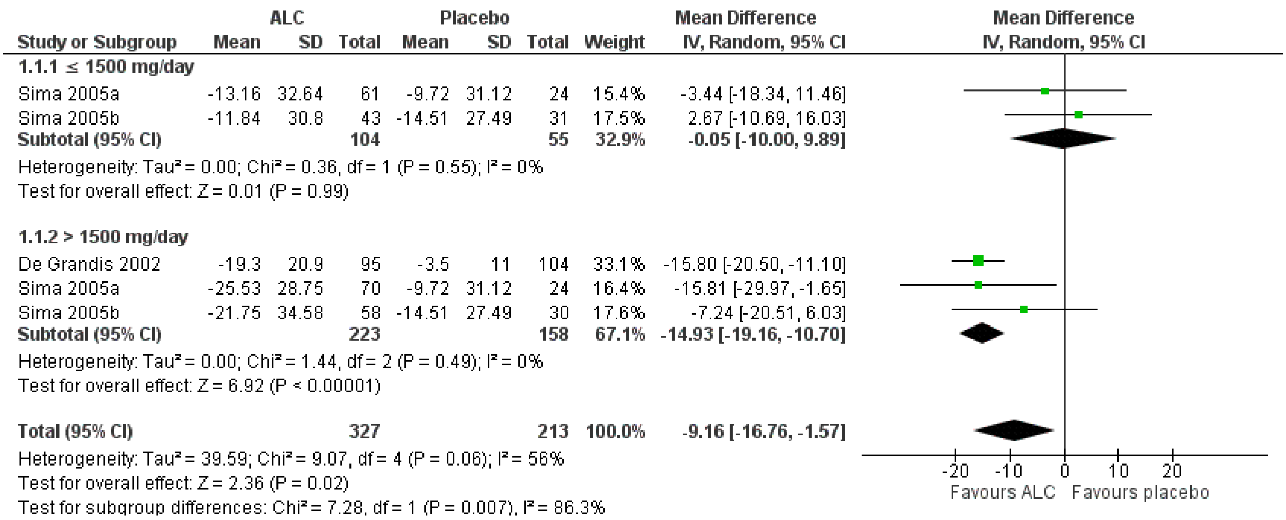
Three studies compared ALC with placebo and reported the results as mean ± standard deviation (SD) (De Grandis 2002; Sima 2005a; Sima 2005b). See Summary of findings for the main comparison.

Primary outcome: pain

We had planned to evaluate this outcome as the proportion of participants with a moderate (30%) or substantial (50%) improvement in pain, but this was not possible with the available data.

Three studies comparing ALC and placebo reported pain as an outcome and measured it using a visual analogue scale (0 to 100 mm, on which higher scores indicate worse pain) (De Grandis 2002; Sima 2005a; Sima 2005b). At 6- to 12-months' follow-up, the mean change in pain from baseline favoured ALC over placebo (MD -9.16, 95% CI -16.76 to -1.57; three studies; 540 participants; I^2 = 56%; random-effects; Analysis 1.1; Figure 3).

Figure 3. Forest plot of comparison: 1 Acetyl-L-carnitine versus placebo, outcome: 1.1 Pain at 6 to 12 months' follow-up.



We judged the certainty of evidence to be very low, because of study limitations, indirectness (as ALC does not have a direct function on pain relief and pain was reported as a mean change), inconsistency of effect (possibly owing to differences in ALC dose), and imprecision.

Subgroup analysis

In the subgroup analysis, we observed that the combined pain results of the subgroup that received over 1500 mg/day ALC favoured ALC over placebo at 6 to 12 months' follow-up, without heterogeneity (MD -14.93, 95% CI: -19.16 to -10.70; three studies; 381 participants; I^2 = 0%; Analysis 1.1; Figure 3). The subgroup of participants who received 1500 mg/day or less did not show a clear difference between ALC and placebo in pain at 12 months' follow-up (MD -0.05, 95% CI: -10.00 to 9.89; two studies; 159 participants; I^2 = 0%). Statistical tests for subgroup differences revealed a significant difference between the over 1500 mg/day subgroup and the below 1500 mg/day subgroup, which was also reflected in the high heterogeneity (Chi^2 = 7.28, df = 1 (P = 0.007), I^2 = 86.3%). These analyses included very few trials and should be interpreted very cautiously.

We were not able to carry out other subgroup and sensitivity analyses because the reports did not provide enough data.

Secondary outcomes

Functional impairment and disability

The included studies did not measure this outcome.

Impairment of sensation

Sima 2005a and Sima 2005b reported this outcome, but incompletely. The study authors reported partial results from the two multicenter studies in the same paper. According to the study authors, at 12 months' follow-up, the group that received ALC 3000 mg/day had better vibration perception in the fingers compared to the placebo group (no total numerical data provided; O'Brien's rank scores). We graded this evidence as very low certainty due to very serious study limitations (the included studies were at high risk of reporting bias as no total numerical data were available). The trials were not reported separately and we do not know if the results were consistent. Therefore, we must be very uncertain about the estimate.

Quality of life

The included studies did not measure this outcome.

Neurophysiological measures

In De Grandis 2002, the trial authors reported that the ALC group had more improvement in sensory nerve conduction velocity (SNCV) and motor nerve conduction velocity (MNCV) at 12 month' follow-up than the placebo group. Note that the quoted P values are those of the trial authors and do no take multiple testing into account. See Table 1.

In De Grandis 2002, ALC also significantly improved sural and median sensory nerve amplitudes and median, ulnar, and peroneal motor nerve amplitudes, when compared with placebo. See Table 2.

Sima 2005a and Sima 2005b reported that in participants taking 1500 mg/day or 3000 mg/day of ALC, none of the NCV or amplitude measures showed any significant changes compared to the placebo group; however, the trial authors did not provide numerical data.

The neurophysiological results should be viewed with caution, since there is no information about the total number of participants evaluated, and no numerical data in Sima 2005a and Sima 2005b. Further, there was a 41.7% loss to follow-up for this outcome (results are reported for only 194 of 333 participants) in De Grandis 2002. It is uncertain whether changes of the reported magnitude have any clinical relevance.

Adverse events

In De Grandis 2002, six participants from the intervention group (6/147, 4.1%) and two from the placebo group (2/147, 1.4%) discontinued treatment due to adverse events. The reasons included headache, facial paraesthesia, and gastrointestinal disorders. There were no clear differences between the tolerability of ALC and placebo either on participants' or investigators' evaluations.

Sima 2005a and Sima 2005b reported that the most common adverse events were pain, paraesthesia, and hyperaesthesias, but there were no dropouts due to adverse events. Fewer participants taking 3000 mg/day of ALC than participants taking placebo reported pain, paraesthesia, and hyperaesthesia. The trial authors reported that there were nine deaths, which were not related to drug treatment, and that the other dropouts were due to withdrawal of consent and protocol violation. The report did not provide any additional numerical data about adverse events.

We assessed the certainty of evidence for the adverse event outcome as low, downgrading twice for study limitations (unclear risk of bias in multiple domains and a high risk of reporting bias in the absence of numerical data). We could not assess precision in the absence of numerical data. The two trials were not reported separately and we do not know if the results were consistent.

Symptom quality and severity

Sima 2005a and Sima 2005b assessed symptoms, but did not use a validated scale. De Grandis 2002 provided no data for this outcome.

Sural nerve biopsy parameters

In Sima 2005a and Sima 2005b, morphometric evaluations of sural nerve biopsies revealed a significant improvement in all biopsy parameters in the group who received 1500 mg/day ALC, compared to placebo (144.1 ± 28.9 versus 132.6 ± 37.8; P = 0.027, O'Brien rank score), with a significant increase in fibre numbers (-14 ± 197 versus -98 ± 352; P = 0.049), and a significantly greater number of regenerating clusters (-3.3 ± 8.0 versus -27.9 ± 9.1; P = 0.033). However, for participants treated with ALC 3000 mg/day, there were no clear differences compared with placebo (the reports did not provide any numerical data). This finding was despite the decreased pain with higher doses. These biopsy-related results were at a high risk of bias, since the sample comprised only 245 pairs of biopsies from 1335 randomised participants and European participants, who did not contribute samples, had different baseline characteristics than the North American participants.

Acetyl-L-carnitine versus methylcobalamin

One study compared ALC (≤ 1500 mg/day) with methylcobalamin (0.5 mg three times per day) (Li 2016). The trial authors tested an equivalence hypothesis of the two interventions for the treatment of diabetic neuropathy, and provided all numerical data as a mean ± SD. See Summary of findings 2.

Primary outcomes: pain

The included study did not measure this outcome.

Secondary outcomes

Functional impairment and disability

In Li 2016, participants from both groups had significant reductions in the NDS (range from zero to 10), compared to their respective baseline measurements (ALC, from 6.58 ± 2.19 to 5.55 ± 2.50, 117 participants; methylcobalamin, from 6.43 ± 2.04 to 5.08 ± 2.41, 115 participants), with no clear difference between the ALC and methylcobalamin groups at 24 weeks' follow-up (ALC 1.66 ± 1.90 versus methylcobalamin 1.35 ± 1.65). This represents a MD of 0.31, 95% CI -0.15 to 0.77 (see Analysis 2.1).

We downgraded the certainty of evidence twice: once for imprecision, as the evidence is from a single study involving 232 participants, and once for indirectness, as methylcobalamin is not an established treatment for DPN. The effects of methylcobalamin are uncertain, which makes it difficult to determine the effects of ALC.

Measures of impairment of sensation

The included study did not measure this outcome.

Quality of life

The included study did not measure this outcome.

Neurophysiological measures

Li 2016 assessed the SNCV and MNCV in the median and ulnar nerves, the sural SNCV, and the tibial and peroneal MNCVs. The trial reported that only the ulnar MNCV showed a statistically significant improvement with ALC in comparison to methylcobalamin after 24 weeks. The results in Table 3 show the changes from baseline to week 24 for the two groups.

Li 2016 assessed action potential amplitudes in the same nerves. Only the ulnar sensory nerve amplitude showed a statistically significant improvement with ALC compared to methylcobalamin (88 participants). It is important to note that Li 2016 considered a level of statistical significance of $P < 0.025$. The results in Table 4 are presented as mean change ± SD or mean (95% CI), and describe the change from baseline to week 24 for the two groups.

Adverse events

In Li 2016, the proportion of participants reporting adverse events was similar in the ALC group (34/117, 29.1%) and the methylcobalamin group (33/115, 28.7%) (RR 1.01, 95% CI 0.68 to 1.52; 232 participants; Analysis 2.2). Four participants from the ALC group, and five from the methylcobalamin group had serious adverse events (RR 0.79, 95% CI 0.22 to 2.85; 232 participants; Analysis 2.3). Four participants from the ALC group and five from the methylcobalamin group discontinued treatment due to adverse events (RR 0.79, 95% CI 0.22 to 2.85; 232 participants; Analysis 2.4). The most common adverse events in both groups were gastrointestinal symptoms, such as abdominal distension, hiccups, and nausea.

We judged the certainty of evidence to be low, downgrading once for imprecision, as the evidence was from a single study of 232 participants, and once for indirectness, as the comparator made it difficult to distinguish the adverse effects of ALC.

Symptom quality and severity

Li 2016 measured symptoms using the Neuropathy Symptom Scale (NSS; a scale from zero to 9, on which a higher score indicates worse symptoms).

In Li 2016, participants in both groups had significant reductions in NSS from baseline to 24 weeks' follow-up (ALC, from 6.52 ± 1.52 to 4.17 ± 2.45, 117 participants, $P < 0.0001$; methylcobalamin, from 6.37 ± 1.71 to 4.25 ± 2.60, 115 participants, $P < 0.0001$), with little difference between the ALC and methylcobalamin groups (2.35 ± 2.23 versus 2.11 ± 2.48, respectively; $P = 0.38$), for a MD of 0.24, 95% CI -0.37 to 0.85; Analysis 2.5).

We downgraded the certainty of evidence twice: once for imprecision, as the evidence is from a single study involving 232 participants, and once for indirectness, as methylcobalamin is not an established treatment for DPN and, therefore, it is difficult to determine the effects of ALC from this study.

Sural nerve biopsy parameters

The included study did not measure this outcome.

DISCUSSION

Summary of main results

Three publications, describing four studies with a total of 907 randomised participants, were eligible for inclusion in this review.

The two comparisons in the included studies were: 1) acetyl-L-carnitine (ALC) versus placebo (three studies, 675 participants) and 2) ALC versus methylcobalamin (one study, 232 participants).

For the primary outcome, it was uncertain whether ALC (all doses) reduced pain compared to placebo, measured on a visual analogue scale (VAS). Doses higher than 1500 mg/day seemed to reduce pain more than placebo (three studies, 675 participants), while the subgroup of participants treated with 1500 mg/day showed little or no reduction in mean pain score compared to placebo (two studies, 159 participants). However, there were few studies and this subgroup analysis may not be reliable. The evidence was very uncertain for changes in measures of impairment, and symptom quality and severity.

We identified no clear differences in adverse events or dropout rates between the ALC and placebo groups; however, the certainty of evidence was low, as data were limited and dropout rates were substantial, where reported. Two studies reported small numerical increases in nerve conduction velocity (NCV) in the ALC group versus placebo after 48 weeks of treatment (versus placebo) or versus methylcobalamin after 24 weeks of treatment. It is worth remembering that NCV is one of the main tests used to evaluate drug efficacy in DPN. However, it may not translate into any clinically useful effect, as it is an indirect measure of neuropathy improvement and can be influenced by multiple factors.

Li 2016 compared ALC with methylcobalamin. This trial did not assess pain. Data indicated little or no difference between the groups on measures of functional impairment and disability or the results of sural nerve biopsy. The adverse event data were also similar between the intervention groups. Although only 4/117 participants receiving ALC and 5/115 participants receiving methylcobalamin discontinued treatment because of adverse events, a considerable number of participants in both groups (29.1% in the ALC group and 28.7% in the methylcobalamin group) reported adverse events.

Overall completeness and applicability of evidence

This review primarily assessed whether ALC reduced pain in people with DPN. It also evaluated other parameters of neural function (functional impairment, measures of impairment of sensation, neurophysiological measures, and sural nerve biopsy parameters), quality of life, quality and severity of symptoms, and safety (adverse events).

Three studies (540 participants) examined ALC versus placebo for the treatment of DPN, within apparently similar study populations. All three analysed and reported the primary outcome and some secondary outcomes prespecified in the protocol of this review (Rolim 2014). They did not use validated scales to assess functional impairment and disability or symptom quality and severity, and did not measure quality of life.

Heterogeneity was high in the ALC versus placebo comparison, mainly owing to the use of a low dose of the drug (1500 mg/day) in subgroups of participants in two studies (Sima 2005a; Sima 2005b). Moreover, Sima and colleagues did not evaluate all outcomes in all enrolled participants, and presented incomplete data on participant numbers in each outcome evaluation. The number of included participants in Analysis 1.1 was considerably smaller than the number randomised to each group.

Each study of ALC versus placebo used a similar 10-cm VAS for the primary outcome (pain). They also used similar inclusion criteria, which resulted in almost identical participant populations across studies in this comparison.

We were able to perform a subgroup analysis for doses of 1500 mg/day or less and above 1500 mg/day. The analysis suggested different effects on pain by subgroup: at doses over 1500 mg/day, ALC reduced pain compared to placebo, whereas at doses of 1500 mg/day or less, ALC had no clear effect. However, the data are limited and the evidence is of very low certainty. The data suggested that dose might have accounted for the overall heterogeneity in Analysis 1.1.

Data were available for at least four of our seven secondary outcomes. None of the included studies provided data sufficiently detailed to allow us to conduct a meta-analysis for any of the secondary outcomes. The qualitative evaluation provided limited information, from one included study, that suggested improvement in neurophysiological measures in the ALC group compared to the placebo group. However, the results should be viewed with caution because of a high number of dropouts for these outcomes in De Grandis 2002. Sima 2005a and Sima 2005b did not report the number of participants evaluated for quantitative sensory scores, neurophysiological measures, or sural nerve biopsies. The trial authors evaluated only 245 pairs of sural nerve biopsies from 1335 randomised participants, which reduced our confidence in these results.

Three included placebo-controlled studies provided very low-certainty evidence on adverse events, showing no clear difference between the groups (De Grandis 2002; Sima 2005a; Sima 2005b).

One study compared ALC with another intervention (methylcobalamin) (Li 2016). This study did not provide information about pain (our primary outcome), quantitative sensory testing, quality of life, or sural nerve biopsies. There was limited information regarding four of our seven secondary outcomes, and only two of the neurophysiological measures favoured ALC over with methylcobalamin. Li 2016 explained that the study lacked a placebo comparison because methylcobalamin had already been approved for DPN in China (where the study took place), and so the local ethical committee did not approve a placebo control. However, methylcobalamin is not approved for use in DPN by authorities in other jurisdictions such as the USA (www.accessdata.fda.gov/scripts/cder/daf/index.cfm) or Europe (www.ema.europa.eu/ema/), since there is a lack of evidence addressing the effects of methylcobalamin for the treatment of DPN. Therefore, it is difficult to interpret the finding from Li 2016 that there may be little or no difference between the effects of ALC and methylcobalamin, because it is possible that both interventions have similar effects.

In summary, we lack data:

- of any certainty on the effects of ALC versus placebo at 6 to 12 months;
- on longer-term follow-up, i.e. follow-up for more than one year;
- comparing the effect of ALC on the two main types of diabetes (type 1 and type 2);
- from different populations. There were data from America, Europe, and Asia; however, data from other continents is needed to increase the external validity of the results

Quality of the evidence

We identified three publications, reporting on four studies with a total of 907 participants. Three trials studied ALC versus placebo; in one, the dose of ALC was 2000 mg/day, and in the other two it was 1500 mg/day or 3000 mg/day (675 participants). The risk of bias was high in both trials of different ALC doses and unclear in the ALC 2000 mg/day trial. The fourth trial studied ALC (at ≤ 1500 mg/day) versus methylcobalamin (232 participants) and was at low risk of bias.

For pain after 12 months, we downgraded the certainty of the evidence three times to very low, because there were very serious study limitations, measurement of the outcome was indirect, and the result was imprecise, with a CI that encompassed both little or no effect and a clinically important effect. There was also a high level of heterogeneity in the overall pain analysis, although this may be explained by dosage. Although pain is routinely reported using scores on a rating scale (continuous data), we planned to report a responder analysis (the proportion of participants with substantial and moderate reductions in pain), which is the preferred measure in Cochrane reviews of treatments for neuropathic pain (PaPaS 2011).

Two placebo-controlled studies reported that NCVs and amplitudes did not improve with ALC (≤ 1500 mg/day and > 1500 mg/day), whereas vibration perception improved after 12 months but did not provide numerical data. Another included placebo-controlled study reported a significant statistical improvement favouring the ALC group in terms of NCVs of all investigated nerves; however, only 194 of 333 participants (41.7%) completed the neurophysiological studies at the end of the trial and the figures for neurophysiological improvement are unreliable (De Grandis 2002). The placebo-controlled studies did not assess functional impairment scores. Sima 2005a and Sima 2005b performed sensory testing, but the certainty of evidence was very low due to very serious study limitations. The trials were not reported separately and we do not know if the results were consistent.

The fourth included study compared ALC ≤ 1500 mg/day with methylcobalamin, but did not report effects on pain or sensation. Both groups showed reductions in functional impairment and disability, and improvement in some neurophysiological parameters (NCVs and amplitudes) from baseline to 24 weeks, with no clear differences between the ALC and methylcobalamin groups. We judged the certainty of evidence to be very low for all reported outcomes, downgrading it once for indirectness and twice for imprecision.

In one placebo-controlled study, eight participants discontinued the treatment due to adverse events (six in the ALC group and two in the placebo group). The two other placebo-controlled studies reported no dropouts due to adverse events, and more adverse events in the placebo group than the ALC > 1500 mg/day group (without numerical data). The overall certainty of the evidence on adverse events for the comparison of ALC versus placebo was low.

The study comparing ALC with methylcobalamin also reported dropouts due to adverse events, with no clear difference between the ALC ≤ 1500 mg/day group (4 participants) and the methylcobalamin group (5 participants). We assessed the certainty of the evidence on adverse events for the comparison of ALC versus methylcobalamin as low; we downgraded it once for imprecision and once for indirectness.

All included studies involved the manufacturers of ALC. Two were clearly funded, and the other two had at least one co-author who was a consultant for an ALC manufacturer.

Potential biases in the review process

We believe that we identified and included all relevant studies. We identified duplicate reports of studies in the selection process and searched multiple sources, with no language restriction. However, the possibility remains that we may have missed some trials, particularly in the grey literature. We adhered to the inclusion and exclusion criteria prespecified in the protocol in order to limit subjectivity (Rolim 2014). We made efforts to obtain additional relevant data from study authors, but were unable to do so. If we can source supplementary data, we will consider them in future updates. We followed standard methodological procedures to reduce bias in the review process.

It should be noted that reviews that include a small number of trials, such as ours, have limitations in relation to events that occur infrequently, such as adverse events.

Agreements and disagreements with other studies or reviews

We identified two published systematic reviews, including one meta-analysis reporting on the effects of ALC for the treatment of DPN.

Li 2015 reviewed the efficacy and safety of ALC for the treatment of people with peripheral neuropathic pain. In contrast with our review, Li 2015 only evaluated pain and included three of the studies (384 participants) included in our review (De Grandis 2002; Sima 2005a; Sima 2005b). Li 2015 only included studies published in English. Li and colleagues concluded that ALC had a moderate effect on reducing pain, as measured on a VAS, in people with peripheral neuropathic pain, and that there was acceptable safety associated with the treatment, despite the fact that the evidence was too limited to draw a definitive conclusion. Our conclusions are more circumspect.

Veronese 2017 investigated six studies, which included 711 participants with DPN (with Sima 2005a and Sima 2005b counted as a single study). In addition to the RCTs analysed in our review (De Grandis 2002; Li 2016; Sima 2005a; Sima 2005b), the authors included three observational studies without a control group, which were conducted in Turkey. These studies involved 53 participants with type 1 and type 2 diabetes. Their median follow-up period was short (8 weeks, range two to 40 weeks). The Veronese 2017 review was funded by an unrestricted grant from Sigma-Tau. Although the authors of Veronese 2017 concluded that ALC seemed to be effective in reducing pain due to DPN and improving electromyographic parameters, the meta-analysis combined pain data from all the trials in our review, including the comparison of ALC and methylcobalamin, and included very substantial heterogeneity (I^2 = 86%). The authors of Veronese 2017 found the trials at low risk of bias using the Jadad scale; which is not consistent with our assessments of high risk for Sima 2005a and Sima 2005b, and unclear risk for De Grandis 2002, using the Cochrane 'Risk of bias tool'. Furthermore, potential changes in nerve temperature (as described by Zochodne 2016) could explain the improvement in NCV that was found in Veronese 2017. The dosage of ALC was highly variable among the studies, and some participants received L-carnitine and not acetyl-L-carnitine. The bioavailability of ALC is better than that of L-carnitine because the acetyl group enables the ALC molecule to cross the blood-brain barrier more easily. In addition, ALC can also provide more acetyl groups for the synthesis of acetylcholine, a crucial neurotransmitter in the nervous system. Taking into consideration these weaknesses, the conclusions of Veronese 2017 regarding ALC and L-carnitine for DPN should be viewed with caution.

AUTHORS' CONCLUSIONS

Implications for practice

It is uncertain whether, in comparison with placebo, acetyl-L-carnitine (ALC) reduces pain in people with diabetic peripheral neuropathy (DPN) after 6 to 12 months; any effect may be present at doses greater than 1500 mg/day but not at lower doses. Data on functional and sensory impairment and symptoms are lacking, or the evidence is of very low certainty. The evidence on adverse events is too uncertain to make any judgements on safety.

Implications for research

The use of ALC for DPN is primarily an attempt to improve poor neurological function due to the metabolic effects of diabetes, and thereby reduce chronic pain. Since pain control is the most relevant outcome for people with diabetes and their clinicians, it is important that future studies of DPN measure pain as a primary outcome, preferably as the proportion of participants with at least moderate (30%) or substantial (50%) pain relief. Future trials need to be large enough to detect effects on clinical outcomes; they should include not only the main clinical outcome of pain, but also measure impairment or disability, sensory function, and symptoms, and use validated scales. Finally, studies need to be of at least two years' duration to assess the long-term effects of ALC. Even though a two-year follow-up is arbitrary, it may be long enough to provide additional data on rare adverse events following ALC treatment, and assess its effects on chronic morbidity. Future trials should include participants with type 1 and type 2 diabetes, and provide individual data by type of diabetes. Continuous outcome data need to be uniform, with use of similar scales, especially for pain and quality of life.

Further studies, with the characteristics suggested above, comparing ALC with a placebo control, remain necessary to evaluate ALC for wider clinical use.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

De Grandis 2002

Methods	Double-blind, randomised, multicentre, placebo-controlled trial
Participants	333 participants (49.8% male) aged ≥18 years (71% aged ≥ 50 years) with type 1 or type 2 diabetes who had been on stable antidiabetic therapy for ≥ 1 year and who met clinical or neurophysiological criteria for DPN, or both
Interventions	Intramuscular ALC (N =167) or placebo (N =166), at a dose of 1000 mg/day for 10 days, and continued orally at a dose of 2000 mg/day for the remainder of the study (355 days)
Outcomes	NCV Sensory and motor nerve amplitudes Pain measured by a VAS
Funding sources	Sigma-Tau ITALY (pharmaceutical industry)
Declarations of interest	None

De Grandis 2002 *(Continued)*

Notes	No information about period over which the trial took place Location: Italy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list that was prepared within each centre
Allocation concealment (selection bias)	Low risk	"The investigators received a set of sealed envelopes, each bearing on the outside only one number"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical 500 mg vials (for intramuscular administration) and 500 mg sachets (for oral administration) containing the active treatment or placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts 39/333 (11.7%). No ITT analyses cited
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Appeared to be free of other sources of bias

Li 2016

Methods	Double-blind, randomised, non-inferiority, multicentre clinical trial
Participants	232 participants (52.5% male) randomised to receive either ALC (N = 117) or methylcobalamin (N = 115). Participants with type 1 or type 2 diabetes mellitus were eligible if they were aged between 18 and 70 years (mean age 57.8 years), had been diagnosed with DPN according to electrodiagnostic criteria from the San Antonio Conference, and had abnormal nerve conduction velocity or amplitude, or both, in at least one nerve of the extremities.
Interventions	ALC 500 mg three times per day (N = 117) or methylcobalamin 0.5 mg three times per day (N = 115) orally for 24 weeks
Outcomes	Changes in the neuropathic symptom and sign scores from baseline to week 24, assessed by the Neuropathy Symptom Score (NSS) Neuropathy Disability Score (NDS) Change in the NCV and amplitude from baseline to week 24 Reversal rates of affected nerves at week 24 Safety endpoints included incidence and intensity of adverse events, and withdrawals due to adverse events

Li 2016 *(Continued)*

Funding sources	Liaoning Haisike Pharmaceutical Co.
Declarations of interest	The authors declared no conflict of interest
Notes	Conducted between August 2008 and March 2011 Location: eight centres in China Clinical trial id: ChiCTR-TRC-08000141

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Each centre produced computer-generated randomisation lists
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes were assigned to participants by physicians, according to the sequence of entry to the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study Quote: "participants and investigators were masked to treatment assignment throughout the study" Quote: "ALC, MC and dummy tablets were identical in appearance"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators assessing nerve conduction and conducting blood tests were blind to the intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts: 28/232 participants (12%). ITT analyses were performed. Quote: "The FAS [full analysis set] population included all randomised patients receiving at least one dose of study treatment, and the last observation carried forward approach was used to impute missing data."
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Appeared to be free of other sources of bias

Sima 2005a

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Two studies enrolled 1346 participants (1335 of whom were randomised), aged between 18 and 70 years, with diabetes (type 1 or 2) and DPN for more than one year, diagnosed according to the San Antonio criteria. No details were given regarding age or gender (Sima 2005a and Sima 2005b)
Interventions	ALC: 1500 mg/day, 3000 mg/day, or placebo for one year. No information about size of each group
Outcomes	Morphometric analyses of sural nerves Electrophysiological parameters Vibration perception

Sima 2005a *(Continued)*

	Clinical symptoms score Participant-reported VAS for pain, in those who reported pain as their most bothersome symptom at baseline (on 342 patients (26.7%))
Funding sources	Not reported
Declarations of interest	Not declared but one of the trial authors (AAFS) was a consultant for Sigma-Tau (ALC manufacturer) and two others had Sigma-Tau affiliations
Notes	Multicentre: 28 centres in USA and Canada No information about period over which the study was conducted Some results of the two trials by Sima and colleagues were reported together (Sima 2005a; Sima 2005b)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as "double-blind, placebo-controlled"; no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as "double-blind, placebo-controlled" "A central reading center was established for all electrophysiological recordings". Insufficient information to determine whether outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	1346 participants were enrolled (1335 randomised); these participants underwent examinations including sural NCV and "patients had to have a detectable sural NCV (≥ 1 μV) to meet the entrance criteria." Quotes: "The population monitored for safety reasons was 1,335 patients or 99.2% of enrolled patients." "Intention-to-treat patients amounted to 1257 or 93% of enrolled participants" Where electrophysiological data were missing, the '1st percentile procedure' was used and for all other data, the last observation was carried forward. "All patients who received at least one dose of the study medication and had one valid post-randomization electromyography assessment were included." "Evaluation of the effect of ALC on neuropathic pain was performed on 342 patients (26.7%) who at baseline reported pain as their most bothersome symptom". Pain analysis was ITT. A low risk of attrition bias in this analysis.

Sima 2005a *(Continued)*

		Quote: "For logistic reasons, sural nerve biopsies were obtained from U.S. or Canadian patients only from both studies. Of patients who underwent a baseline biopsy, 87% had a second biopsy, yielding 245 evaluable pairs of biopsies." This represents a high risk of bias - these participants had different characteristics from the participants in the European studies.
Selective reporting (reporting bias)	High risk	Three efficacy outcomes reported incompletely. Measures of impairment of sensation: no total numerical data provided. Neurophysiological measures: no total numerical data provided. Sural nerve biopsy parameters: only 245 pairs of biopsies in 1335 randomised participants.
Other bias	Unclear risk	Quote: "Evaluation of the effect of ALC on neuropathic pain was performed on 342 patients (26.7%) who at baseline reported pain as their most bothersome symptom" As it is unclear whether blinding and allocation concealment were adequate, knowledge of intervention groups could, in principle, have influenced inclusion of participants in the pain analysis. Therefore, we considered that these studies were at unclear risk of other bias in relation to the effects of ALC on pain.

Sima 2005b

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Two studies enrolled 1346 participants (1335 of whom were randomised), aged between 18 and 70 years, with diabetes (type 1 or 2) and DPN for more than one year, diagnosed according to the San Antonio criteria. No details were given regarding age or gender (Sima 2005a and Sima 2005b).
Interventions	ALC: 1500 mg/day, 3000 mg/day, or placebo for one year. No information about size of each group
Outcomes	Morphometric analyses of sural nerves Electrophysiological parameters Vibration perception Clinical symptoms score Participant-reported VAS for pain in those who reported pain as their most bothersome symptom at baseline (on 342 patients (26.7%))
Funding sources	Not reported
Declarations of interest	Not declared, but one of the trial authors (AAFS) was a consultant for Sigma-Tau (ALC manufacturer) and two others had Sigma-Tau affiliations
Notes	Multicentre: 34 centres in USA, Canada, and Europe No information about period over which the study was conducted Some results of two trials by Sima and colleagues were reported together (Sima 2005a; Sima 2005b)
Risk of bias	

Sima 2005b *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as "double-blind, placebo-controlled"; no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as "double-blind, placebo-controlled" "A central reading center was established for all electrophysiological recordings". Insufficient information to determine whether outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	1346 participants were enrolled (1335 randomised); these participants underwent examinations including sural NCV and "patients had to have a detectable sural NCV (≥ 1 μV) to meet the entrance criteria" Quotes: "The population monitored for safety reasons was 1335 patients or 99.2% of enrolled patients." Comment: low risk of attrition bias "Intention-to-treat patients amounted to 1257 or 93% of enrolled participants" Where electrophysiological data were missing, the '1st percentile procedure' was used, and for all other data, the last observation was carried forward. "All patients who received at least one dose of the study medication and had one valid post-randomization electromyography assessment were included." "Evaluation of the effect of ALC on neuropathic pain was performed on 342 patients (26.7%) who at baseline reported pain as their most bothersome symptom". Pain analysis was ITT. A low risk of attrition bias in this analysis Quote: "For logistic reasons, sural nerve biopsies were obtained from U.S. or Canadian patients only from both studies. Of patients who underwent a baseline biopsy, 87% had a second biopsy, yielding 245 evaluable pairs of biopsies." This represented a high risk of bias - these participants had different characteristics from the participants in the European studies.
Selective reporting (reporting bias)	High risk	Three efficacy outcomes reported incompletely Measures of impairment of sensation: no total numerical data provided Neurophysiological measures: no total numerical data provided Sural nerve biopsy parameters: only 245 pairs of biopsies in 1335 randomised participants
Other bias	Unclear risk	Quote: "Evaluation of the effect of ALC on neuropathic pain was performed on 342 patients (26.7%) who at baseline reported pain as their most bothersome symptom" As it is unclear whether blinding and allocation concealment were adequate, knowledge of intervention groups could, in principle, have influenced inclusion of participants in the pain analysis. Therefore, we considered that these

Sima 2005b *(Continued)*

	studies were at unclear risk of other bias in relation to the effects of ALC on pain.

ALC: acetyl-L-carnitine; DPN: diabetic peripheral neuropathy; ITT: intention-to-treat; N: number of participants; NCV: nerve conduction velocity; VAS: visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbott 1997	ALC for prevention of diabetic foot ulceration
Quatraro 1995	The duration of the study was only 15 days, and it was a pilot study with a small number of participants (20). Moreover, 65% of participants were on insulin treatment, and glycaemic control was not reported either before or after the trial.

ALC: acetyl-L-carnitine

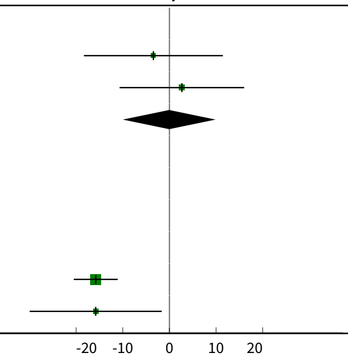
DATA AND ANALYSES

Comparison 1. Acetyl-L-carnitine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain at 6 to 12 months' follow-up	3	540	Mean Difference (IV, Random, 95% CI)	-9.16 [-16.76, -1.57]
1.1 ≤ 1500 mg/day	2	159	Mean Difference (IV, Random, 95% CI)	-0.05 [-8.00, 9.89]
1.2 > 1500 mg/day	3	381	Mean Difference (IV, Random, 95% CI)	-14.93 [-19.16, -10.70]

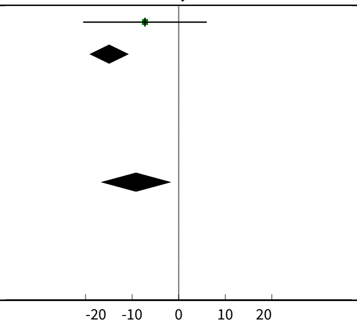
Analysis 1.1. Comparison 1 Acetyl-L-carnitine versus placebo, Outcome 1 Pain at 6 to 12 months' follow-up.

Study or subgroup	ALC N	ALC Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.1.1 ≤ 1500 mg/day							
Sima 2005a	61	-13.2 (32.6)	24	-9.7 (31.1)		15.43%	-3.44[-18.34,11.46]
Sima 2005b	43	-11.8 (30.8)	31	-14.5 (27.5)		17.47%	2.67[-10.69,16.03]
Subtotal ***	**104**		**55**			**32.89%**	**-0.05[-10,9.89]**
Heterogeneity: Tau^2=0; Chi^2=0.36, df=1(P=0.55); I^2=0%							
Test for overall effect: Z=0.01(P=0.99)							
1.1.2 > 1500 mg/day							
De Grandis 2002	95	-19.3 (20.9)	104	-3.5 (11)		33.13%	-15.8[-20.5,-11.1]
Sima 2005a	70	-25.5 (28.8)	24	-9.7 (31.1)		16.38%	-15.81[-29.97,-1.65]



Favours ALC | Favours placebo

Study or subgroup	ALC		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Sima 2005b	58	-21.7 (34.6)	30	-14.5 (27.5)		17.6%	-7.24[-20.51,6.03]
Subtotal ***	**223**		**158**			**67.11%**	**-14.93[-19.16,-10.7]**
Heterogeneity: Tau²=0; Chi²=1.44, df=2(P=0.49); I²=0%							
Test for overall effect: Z=6.92(P<0.0001)							
Total ***	**327**		**213**			**100%**	**-9.16[-16.76,-1.57]**
Heterogeneity: Tau²=39.59; Chi²=9.07, df=4(P=0.06); I²=55.92%							
Test for overall effect: Z=2.36(P=0.02)							
Test for subgroup differences: Chi²=7.28, df=1 (P=0.01), I²=86.26%							

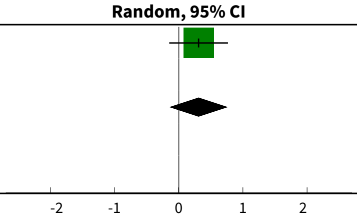


Comparison 2. Acetyl-L-carnitine versus methylcobalamin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Functional impairment and disability (change in Neurological Disability Scale) at 24 weeks' follow-up	1	232	Mean Difference (IV, Random, 95% CI)	0.31 [-0.15, 0.77]
2 Adverse events	1	232	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.68, 1.52]
3 Serious adverse events	1	232	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.22, 2.85]
4 Adverse events leading to withdrawal	1	232	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.22, 2.85]
5 Symptom quality and severity (change in Neuropathy Symptom Score) at 24 weeks' follow-up	1	232	Mean Difference (IV, Fixed, 95% CI)	0.24 [-0.37, 0.85]

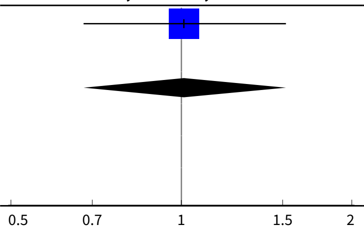
Analysis 2.1. Comparison 2 Acetyl-L-carnitine versus methylcobalamin, Outcome 1 Functional impairment and disability (change in Neurological Disability Scale) at 24 weeks' follow-up.

Study or subgroup	ALC		Methylcobalamin		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Li 2016	117	1.7 (1.9)	115	1.4 (1.7)		100%	0.31[-0.15,0.77]
Total ***	**117**		**115**			**100%**	**0.31[-0.15,0.77]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.33(P=0.18)							



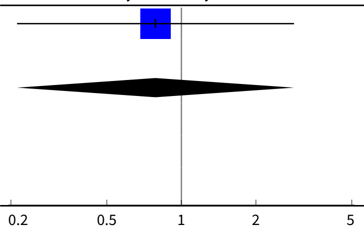
Analysis 2.2. Comparison 2 Acetyl-L-carnitine versus methylcobalamin, Outcome 2 Adverse events.

Study or subgroup	ALC n/N	Methyl-cobalamin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Li 2016	34/117	33/115		100%	1.01[0.68,1.52]
Total (95% CI)	**117**	**115**		**100%**	**1.01[0.68,1.52]**
Total events: 34 (ALC), 33 (Methylcobalamin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.06(P=0.95)					



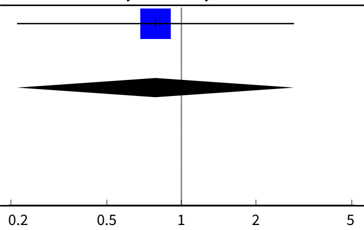
Analysis 2.3. Comparison 2 Acetyl-L-carnitine versus methylcobalamin, Outcome 3 Serious adverse events.

Study or subgroup	ALC n/N	Methyl-cobalamin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Li 2016	4/117	5/115		100%	0.79[0.22,2.85]
Total (95% CI)	**117**	**115**		**100%**	**0.79[0.22,2.85]**
Total events: 4 (ALC), 5 (Methylcobalamin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.37(P=0.71)					



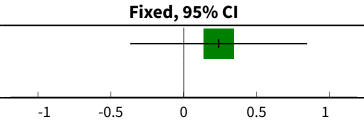
Analysis 2.4. Comparison 2 Acetyl-L-carnitine versus methylcobalamin, Outcome 4 Adverse events leading to withdrawal.

Study or subgroup	ALC n/N	Methyl-cobalamin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Li 2016	4/117	5/115		100%	0.79[0.22,2.85]
Total (95% CI)	**117**	**115**		**100%**	**0.79[0.22,2.85]**
Total events: 4 (ALC), 5 (Methylcobalamin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.37(P=0.71)					

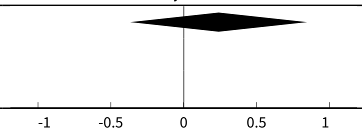


Analysis 2.5. Comparison 2 Acetyl-L-carnitine versus methylcobalamin, Outcome 5 Symptom quality and severity (change in Neuropathy Symptom Score) at 24 weeks' follow-up.

Study or subgroup	ALC N	ALC Mean(SD)	Methylcobalamin N	Methylcobalamin Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Li 2016	117	2.4 (2.2)	115	2.1 (2.5)		100%	0.24[-0.37,0.85]



Study or subgroup	ALC N	ALC Mean(SD)	Methylcobalamin N	Methylcobalamin Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Total ***	**117**		**115**			**100%**	**0.24[-0.37,0.85]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=0.77(P=0.44)							



ADDITIONAL TABLES

Table 1. Nerve conduction velocity measurements at 12 months' follow-up (De Grandis 2002)

Nerve conduction velocity measurements at 12 months' follow-up (De Grandis 2002)

	ALC (> 1500 mg/day)			Placebo			P value
	Mean change (m/s)	SD	Number of participants	Mean change (m/s)	SD	Number of participants	
Ulnar SNCV	2.9	3.2	89	0.1	2.0	74	< 0.01
Sural SNCV	5.7	6.8	51	1.0	2.8	44	< 0.01
Median SNCV	1.7	2.4	17	0.2	1.6	18	< 0.05
Ulnar MNCV	2.3	3.0	93	0.2	3.0	82	< 0.01
Peroneal MNCV	2.7	2.1	82	−0.2	2.2	70	< 0.01
Median MNCV	1.6	3.7	17	−0.9	1.5	15	< 0.01

ALC: acetyl-L-carnitine; MNCV: motor nerve conduction velocity; SD: standard deviation; SNCV: sensory nerve conduction velocity

Table 2. Nerve amplitude measurements at 12 months' follow-up (De Grandis 2002)

Nerve amplitude measurements at 12 months' follow-up (De Grandis 2002)

	ALC (> 1500 mg/day)			Placebo			P value
	Mean change	SD	Number of participants	Mean change	SD	Number of participants	
Ulnar SN (µV)	1.0	0.9	89	−0.2	0.8	74	Not significant (P = not available)
Sural SN (µV)	1.5	1.4	48	0.0	0.8	42	< 0.01
Median SN (µV)	2.3	1.9	17	−0.4	1.7	18	< 0.01
Ulnar MN (mV)	1.4	1.8	80	0.1	1.4	68	< 0.01
Peroneal MN (mV)	2.2	1.9	19	0.1	2.0	13	< 0.01

Table 2. Nerve amplitude measurements at 12 months' follow-up (De Grandis 2002) *(Continued)*

Median MN (mV)	0.8	1.3	12	−0.1	0.3	11	< 0.05

ALC: acetyl-L-carnitine; MN: motor nerve; SD: standard deviation; SN: sensory nerve

Table 3. Nerve conduction velocity measurements at 12 months' follow-up (Li 2016)

Nerve conduction velocity measurements at 12 months' follow-up (Li 2016)

	ALC (≤ 1500 mg/day)			Placebo			P value
	Mean change (m/s)	SD	Number of participants	Mean change (m/s)	SD	Number of participants	
Median SNCV	5.03	10.78	75	6.42	12.73	65	0.57
Ulnar SNCV	5.01	9.76	50	5.72	9.95	41	0.81
Sural SNCV	3.10	5.59	37	2.02	4.10	28	0.40
Median MNCV	3.49	8.40	61	2.11	6.25	55	0.78
Ulnar MNCV	4.49	7.38	50	0.55	5.25	52	0.003
Tibial MNCV	1.72	5.85	40	2.75	5.18	46	0.66
Peroneal MNCV	5.00	10.25	64	2.45	5.36	54	0.45

ALC: acetyl-L-carnitine; MNCV: motor nerve conduction velocity; SD: standard deviation; SNCV: sensory nerve conduction velocity

Table 4. Nerve amplitude measurements at 12 months' follow-up (Li 2016)

Nerve action potential amplitude measurements at 12 months' follow-up (Li 2016)

	ALC (≤ 1500 mg/day)			Placebo			P value
	Mean change	95% CI or SD	Number of participants	Mean change	95% CI or SD	Number of participants	
Median SN (µV)	0.0	−0.07 to 3.60	69	0.0	0.0 to 3.50	62	0.65

Table 4. Nerve amplitude measurements at 12 months' follow-up (Li 2016) *(Continued)*

Ulnar SN (µV)	0.0	−0.30 to 1.35	44	0.50	0.0 to 11.50	44	0.04
Sural SN (µV)	0.0	−0.10 to 1.76	35	0.0	-1.95 to 1.40	18	0.41
Median MN (mV)	1.03	0.0 to 6.08	32	1.53	3.14	23	0.24
Ulnar MN (mV)	1.18	0.0 to 2.71	30	0.40	0.0 to 0.95	25	0.24
Tibial MN (mV)	0.0	−0.15 to 2.46	45	0.45	-0.41 to 3.96	51	0.45
Peroneal MN (mV)	0.0	−0.03 to 1.14	60	0.08	0.0 to 0.88	60	1.0

ALC: acetyl-L-carnitine; CI: confidence interval; MN: motor nerve; SD: standard deviation; SN: sensory nerve

APPENDICES

Appendix 1. Cochrane Neuromuscular Specialised Register (via the Cochrane Register of Studies; CRS-Web) search strategy

#1 diabet* and *carnitine AND INREGISTER

Appendix 2. CENTRAL (via the Cochrane Register of Studies; CRS-Web) search strategy

#1 diabetic and neuropathy and carnitine AND CENTRAL:TARGET

Appendix 3. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
----
1 randomized controlled trial.pt. (463067)
2 controlled clinical trial.pt. (92470)
3 randomized.ab. (414644)
4 placebo.ab. (189833)
5 drug therapy.fs. (2026166)
6 randomly.ab. (292754)
7 trial.ab. (431351)
8 groups.ab. (1807494)
9 or/1-8 (4227789)
10 exp animals/ not humans.sh. (4468559)
11 9 not 10 (3654630)
12 exp Diabetes Mellitus/ (383844)
13 diabet$.mp. (612836)
14 12 or 13 (614610)
15 exp Peripheral Nervous System Diseases/ (136489)
16 15 or (neuropath$ or polyneuropath$).mp. (220681)
17 14 and 16 (25696)
18 Diabetic Neuropathies/ (13714)
19 17 or 18 (25696)
20 Acetylcarnitine/ (1169)
21 (acetylcarnitine or acetyl l carnitine).tw. (1528)
22 levacecarnine.tw. (7)
23 or/20-22 (1786)
24 11 and 19 and 23 (26)
25 remove duplicates from 24 (26)

Appendix 4. Embase (OvidSP) search strategy

Database: Embase <1974 to 2018 June 29>
Search Strategy:
----
1 crossover-procedure.sh. (55930)
2 double-blind procedure.sh. (151259)
3 single-blind procedure.sh. (31699)
4 randomized controlled trial.sh. (507666)
5 (random$ or crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).tw,ot. (1532411)
6 trial.ti. (251985)
7 controlled clinical trial/ (460068)
8 or/1-7 (1844261)
9 exp animal/ or exp invertebrate/ or animal.hw. or non human/ or nonhuman/ (26215106)
10 human/ or human cell/ or human tissue/ or normal human/ (19832234)
11 9 not 10 (6432581)
12 8 not 11 (1640840)
13 exp diabetes mellitus/ (846032)
14 13 or diabet$.tw. (993823)
15 exp peripheral neuropathy/ (64740)

16 (neuropath$ or polyneuropath$ or peripheral nervous system disease$).mp. (298725)
17 15 or 16 (299158)
18 14 and 17 (46377)
19 diabetic neuropathy/ (21861)
20 18 or 19 (46377)
21 acetylcarnitine/ (1286)
22 acetylcarnitine.mp. (1690)
23 acetyl l carnitine.mp. (1103)
24 levacecarnine.mp. (1530)
25 or/21-24 (3183)
26 12 and 20 and 25 (30)
27 remove duplicates from 26 (28)
28 limit 27 to (conference abstracts or embase) (28)

Appendix 5. LILACS (IAHx) search strategy

((diabet* and neuropath*) and (acetylcarnitine or "acetyl l carnitine" or levacecarnine)) and ((PT:"Randomized Controlled Trial" or "Randomized Controlled trial" or "Ensayo Clínico Controlado Aleatorio" or "Ensaio Clínico Controlado Aleatório" or PT:"Controlled Clinical Trial" or "Ensayo Clínico Controlado" or "Ensaio Clínico Controlado" or "Random allocation" or "Distribución Aleatoria" or "Distribuição Aleatória" or randon$ or Randomized or randomly or "double blind" or "duplo-cego" or "duplo-cego" or "single blind" or "simples-cego" or "simples cego" or placebo$ or trial or groups) AND NOT (B01.050$ AND NOT (humans or humanos or humanos)))

Appendix 6. ClinicalTrials.gov search strategy

Condition: diabetic peripheral neuropathy

Intervention: Acetyl L-carnitine OR acetyl carnitine OR levacecarnine

Appendix 7. WHO ICTRP search strategy

Condition: diabetic peripheral neuropathy

Intervention: Acetyl L-carnitine OR acetyl carnitine OR levacecarnine

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: LCSPR and EMKS

Designing the review: LCSPR and EMKS

Co-ordinating the review: SAD

Undertaking manual searches: LCSPR

Screening search results: LCSPR and EMKS

Organising retrieval of papers: LCSPR

Screening retrieved papers against inclusion criteria: LCSPR and EMKS

Appraising risk of bias of trials: LCSPR, EMKS, RLGF, MMA, and SAD

Extracting data from papers: LCSPR and RLGF

Writing to authors of papers for additional information: SAD

Providing additional data about papers: SAD and LCSPR

Obtaining and screening data on unpublished studies: LCSPR

Data management for the review: LCSPR and RLGF

Entering data into Review Manager: EMKS

Data checking: LCSPR and RLGF; study characteristics data checking: SAD, LCSPR, and MMA

Interpretation of data: LCSPR, EMKS, RLGF, MMA, and SAD

Writing the review: LCSPR, EMKS and RLGF

Providing guidance on the review: EMKS, RLGF and MMA

Performing previous work that was the foundation of the present study: none

Guarantor for the review (one author): LCSPR

Person responsible for reading and checking review before submission: LCSPR, EMKS, RLGF, MMA, and SAD

DECLARATIONS OF INTEREST

LCSPR: I gave a lecture on 23 July 2013 about the practical diagnosis of diabetic neuropathy. The talk was prepared by myself without any influence from the funders (Merck Serono).

EMKS: none known

RLGF: none known

MMA: none known

SAD: none known

SOURCES OF SUPPORT

Internal sources

- Cochrane Brazil and the Division of Vascular and Endovascular Surgery, Universidade Federal de Sao Paulo provided support for authors, Brazil.

External sources

- This project was supported by the National Institute for Health Research (NIHR) via Cochrane Infrastructure funding to Cochrane Neuromuscular. Cochrane Neuromuscular is also supported by the MRC Centre for Neuromuscular Diseases, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

One co-author (William Ricardo Komatsu) was unable to contribute to the review after the protocol stage; he is no longer listed as an author. Another author (RLGF) contributed to the final version of this review and was included in the author team.

The objective was amended from 'To evaluate the effectiveness and safety of ALC for the treatment of diabetic polyneuropathy' in the protocol to 'To assess the effects of ALC for the treatment of diabetic peripheral neuropathy' at the review stage, in order to reflect the aim of the review more accurately.

We specified that we followed guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* for 'Risk of bias' summary assessments.

We amended the 'Subgroup analysis and investigation of heterogeneity' section:

- to include the rationale for the included items and remove 'disease severity' item;
- to clarify the method for interpretation of subgroups results;
- in accordance with sections 9.6.6 and 9.6.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions*, and because only two subgroups were available, we looked for subgroup effects by interpretation of the tests for subgroup differences (Deeks 2017).

We revised the thresholds for the interpretation of the I^2 statistic in accordance with current guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

According to our selection criteria, trials that did not meet Toronto Consensus standards for the diagnosis of DPN were not included in the review. We intended to specify sensitivity analyses excluding trials in participants with 'probable DPN', rather than trials in participants with 'possible DPN', and made this correction in the review.

Missing data emerged as an important risk of bias in the review process and we attempted to contact trial authors to obtain additional information. We did not plan to do so when we prepared our original protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetylcarnitine [administration & dosage] [adverse effects] [*therapeutic use]; Diabetes Mellitus, Type 1 [*complications]; Diabetes Mellitus, Type 2 [*complications]; Diabetic Neuropathies [complications] [*drug therapy]; Neuralgia [*drug therapy]; Pain Measurement; Placebos [therapeutic use]; Randomized Controlled Trials as Topic; Sensation [drug effects]; Vibration; Vitamin B 12 [administration & dosage] [analogs & derivatives] [therapeutic use]

MeSH check words

Adult; Aged; Female; Humans; Male; Middle Aged